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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,201	04/02/2002	Michael Chopp	1059.00063	4921

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,201	CHOPP ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SD.

DETAILED ACTION

Response to Arguments

Claims 1-3, 5-8 were amended. Claims 1-8 are presented for reconsideration on the merits.

Applicants' request for reconsideration of the rejection of the claims in the last office action is being considered.

Drawings

The drawings were received on July 06, 2005. These drawings have been considered, and the objection withdrawn.

Claim Rejections - 35 USC § 112

Applicant's arguments, see remarks, filed July 06, 2005, with respect to Claim rejections 35 U.S.C.112-2 have been fully considered and are persuasive. Claims 1 and 5-8 have been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-5 were rejected in the last Office action as being anticipated by Moskowitz US 5,385,940.

Claims 2 - 5 stand rejected under 35 U.S.C. 102(b) as being anticipated by Moskowitz US 5385940.

Claim 2 requires the neuron growth promoting compound to be a nitric oxide donor; claim 3 requires a pharmaceutical carrier; claim 4 recites augmentation in tissue; and, claim 5 recites L-arginine as on such neurogenesis promoter. These claims are directed to a compound and composition. The intended use, promoting neuron growth, does not alter the compound nor the composition. The Moskowitz patent discloses L-arginine (see, e.g., the abstract, column 3) as a nitric oxide releasing compound. Moskowitz also administered an effective amount (10-500mg/kg) at column 3 line 65 that overlapps applicants' invention. The effective amount on page 12 of the specification (10-100mg/kg) is administered. Administering Moskowitz effective amount will thereby cause new neuron growth as claimed, to be therapeutic and have the same function ie., promoting new neurons. Also Moskowitz at column 3 line 30+ discloses treatment to patients at risk of stroke and after completion of a stroke episode (post stroke). Consequently, the reference anticipates the claimed invention defined in claims 2-5. The compound arginine recited in the claims is the same as in the reference. Thus, at page 6 of the response citation of Hybhtech Inc. v. Monoclonal Antibodies and Richardson c. Suzuki Motor Co., Ltd. are unpersuasive. It also noted that at pages 5-12 the response, the argument is directed to a method of use. The currently rejected claims above are directed to the compound/composition claims. Method of use arguments are unpersuasive regarding claims directed to compounds and/or compositions.

If applicants interpretation is different from the prior art by administering the same compound in an effective amount to the same population is not in the claims. Claims 2-5 still stand rejected as the claims are directed to a compound and composition, and the intended use does not alter the compound nor composition.

In response to the applicants remarks filed July 6, 2005 have been fully considered but they are not persuasive. The rejection made over Moskowitz '940 under U.S.C. § 102 (b) is maintained and hereby repeated.

Applicants argument has been given careful consideration but is not persuasive. Moscowitz explicitly teach the compound promoting claims 2 –5. Please note the compound is taught as a compound for treating stroke and the compound recited is the same as in reference ie. L-arginine.

Claims 2, 3 and 4 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hindley et al., reference (J. Neuroscience of research 47:427-239).

A compound from claim 1 for promoting neuron growth comprising an effective amount of NO donor sufficient to promote neurogenesis. Hindley et.al. discloses in the abstract that cell cultures treated with NO donors such as Na-nitropruside contained a greater proportion of cell bearing neutrites. Sodium nitroprusside (SNP) is a known NO donor. Hindley (page 429) teaches culture PC2 cells treated for 48 hours with a combination of NO donors and NGF had twice as many neutrite bearing cells. Thus twice as many is an indication of doubling of cells, indication of new cells, neutrite growth is one of several, elongation of the existing neuron, new growth. The argument presented by applicant is not persuasive. On page 5 lines 20-25 of the instant

application, applicant defines "promoting neurogenesis" as neural growth being promoted or enhanced. This includes new neuronal growth, enhanced growth and proliferation of parenchyma cells that promote tissue plasticity. The term neurogenesis is as defined from the oxford dictionary to be *Neurogenesis*, the development of nervous tissue. The ideas of Harrison..are perfectly applicable to normal neurogenesis as well as to nervous regeneration. investigators of neurogenesis have often turned to older organisms with the fortunate capacity of regenerating amputated nerve fibers. The notion that neurogenesis ends no later than a few months after birth has profound implications for understanding how the primate brain works. Cell-cell signaling through the Notch receptor is a principal mechanism underlying cell fate specification in a variety of developmental processes in metazoans, such as neurogenesis.

Applicants' argument has been considered, but unpersuasive as the term new neuron growth is taught by Hindley et al at page 429.

Claim 2 is rejected under 35 U.S.C. 102(b) as anticipated by either of Nielsen et.al Am. J. of Crit. Care Med. Vol1611154-1160 (2000) or Poluha et al. Journal of Biological Chem. Vol. 272:38 24002-07.

Nielsen teaches that these compounds can be used as alternatives in administering NO donors in the clinical arena that such drugs are equally effective in the treatment of pulmonary hypertension. In the alternative, and as a separate rejection of claim 2, Poluha teaches at column 2 paragraph 1 that NO is a regulatory molecule that influences many processes, including neuronal proliferation and differentiation, that NO acts as a regulator of cell proliferation which in turn influences process outgrowth.

Although Poluha et al., per se did not disclose reaction of SNP in vivo, the reference clearly states at page 24006 that during development the nerve growth factor induced differentiation of PC12 cells and serves as a prototype for the additional pathways that regulate cell proliferation during differentiation and response to stimuli such as injury hence stroke is an injury. Page 24005 Poluha et al disclose that the effects of NO include elevated levels of p53 a protein required for NGF-induced neuritogenesis of PC12 cells (neuritogenesis- growth on neutrites).

Applicants argument is unpersuasive because of the reasons stated above.

Claim 5 rejected under 35 U.S.C. 102(b) as anticipated by Schipp et al., (Invert. Neurosci 4:9-15 1999) is withdrawn.

Applicants' argument was persuasive, and the rejection is withdrawn.

Claim Rejections - 35 USC § 103

Claims 1 and 6 stand rejected under U.S.C. § 103(a) as being unpatentable over Moskowitz patent ('940) taken with Poluha et al and Adams, et al.

Applicants argument filed July 06, 2005 have been fully considered but they are not persuasive. The rejection made in the last office action over Moskowitz '940 taken with Poluha and Adams is maintained and hereby repeated.

Moskowitz teaches the method of administering the drug can be delivered in any way such as intravascular infusion column 2 line 46. In the specification it is mentioned that the compound can be administered in various ways (page 9 of spec) such as intravenous infusion.

Moskowitz also teaches that l-arginine is a NO donor, however it does not per se teach the promotion of neural growth, the result however is known to give an outgrowth of neuron as taught by Poluha et al. which is cited here to show a fact, namely that administering NO is known prior to the time the claimed invention was made, to result in neural outgrowth in cells. Thus, one of ordinary skill in the art would have been motivated to have added NO to promote neural outgrowth as a well as for treatment of stroke where neurological impairment is a noted result (Moskowitz column 1, lines 10-30). The term patient in the claim can be taken to mean any mammalian patient as described in column 2 line 33 of Moskowitz.

It is mentioned that the compound is administered to someone who has had a stroke or administered post stroke (column 3, lines 39+). Moskowitz teaches that L-arginine can be administered to a stroke patient, either before, during, or after the stroke column 2 line 19. While Moskowitz et al. at (column 3, lines 44+) refer to routes of administration that include topical one of ordinary skill in the art would have been aware of and known NO is delivered to various sites needing "augmentation" (sites needing neural outgrowth or increased neurological function). Here, as combined, Adams et al. teaches that systematic routes for administering NO can be through oral, parenteral, intracisternal, transcutaneus (by injection or by patch) intravenous, intramuscular, buccal, or oral spray column 7 line 30. Adams et al also teaches that in a preferred embodiment a method of reversing pathologenic vascular degradative modeling in the ilio-hypogastric-prudendal arterial bed and genitalia NO donors and phosphodiesterase inhibitors can be administered to a patient in need (abstract). Here, one of ordinary skill

in the art would have combined the teachings in the Moskowitz reference (col 2, lines 5+) that "the nitric oxide releasing compound is L-arginine.

L-arginine is a precursor for nitric oxide synthase, which transforms arginine into NO and citrulline", with that of Poluha et al. which teaches NO administration results in neural proliferation (page 24002, left column) with Adams et al, (abstract) and demonstrates the result of NO administration as taught by Moskowitz. Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Moskowitz at column 3 line 30+ discloses treatment to patients at risk of stroke and after completion of a stroke episode (post stroke). Consequently, the reference teaches the claimed invention defined in claims 1and 6.

Moskowitz explicitly teach administration of the nitric oxide donor to patients at risk (indicating before) and after an episode of stroke (post-stroke) column 3 lines 25+. Administering an effective amount is taught at column 3 line 55+. Moskowitz teaches the method of administering the drug can be delivered in any way such as intravascular infusion column 2 line 46. In the specification it is mentioned that the compound can be administered in various ways (page 9 of spec) such as intravenous infusion.

Moskowitz also teaches that l-arginine is a NO donor, however it does not per se teach the promotion of neural growth, the result however is known to give an outgrowth of neuron as taught by Poluha et al. which is cited here to show a fact, namely that administering NO is known prior to the time the claimed invention was made, to result in neural outgrowth in cells. Thus, one of ordinary skill in the art would also have found it

obvious to combine the Moskowitz, Poluha et al., and Adams et al. teachings administering NO to effect neural growth with those of Van Wagenen et al.

Applicants' argument is unpersuasive since the compound taught is a NO donor and has been known in the prior art, before the claimed invention was made, would motivate one of ordinary to use any NO donor and achieve the claimed invention.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moskowitz US 5385940, taken with Poluha et al. Journal of Biological Chem. Vol. 272:38 24002-07, and Adams et al. US 6,284763 as applied to claims I and 6 above, and further in view of. Van Waqenen.

Moskowitz, Poluha et al, and Adams are applied here as indicated above from the immediately preceding rejection. In addition where claims 7 and 8, refer to increased neurological function via neuron growth.

One of ordinary skill in the ad would because Van Wagenen et al. teach that growth cones are the motile tips of outgrowing axons and dendrites that serve as both sensory and motor function because stimuli that influence filopdial length, number, and modality are likely to affect neuronal path finding and that of Thompson teachings that topical l-arginine is a sensitizing agent produced from intracellular nitric acid, which is a potent vasodilator of smooth muscles. Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

The applicants' argument is unpersuasive because of the same reasons given above.

No claims are allowed.

Please note that absent definition in the specification and claims, one of of skill in the art would have used the definition from

1900 W. A. N. DORLAND *Med. Dict.* 441/2 *Neurogenesis*, the development of nervous tissue. **1908** *Jrnl. Royal Microsc. Soc.* 27 Arguments based on embryonic neurogenesis. **1928** R. M. MAY tr. S. Ramón y Cajal *Degeneration & Regeneration Nerv. Syst.* I. xvi. 381 The ideas of Harrison..are perfectly applicable to normal neurogenesis as well as to nervous regeneration. **1967** M. V. EDDS in G. C. Quarton et al. *Neurosciences: Study Program* 232/1 Faced with the limitations imposed by working with the embryo, investigators of neurogenesis have often turned to older organisms with the fortunate capacity of regenerating amputated nerve fibers. **1985** *Sci. Amer.* May 57/3 The notion that neurogenesis ends no later than a few months after birth has profound implications for understanding how the primate brain works. **2000** *Development* **127** 291 Cell-cell signaling through the Notch receptor is a principal mechanism underlying cell fate specification in a variety of developmental processes in metazoans, such as neurogenesis.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SVG
8/18/05

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